

## **REMARKS**

Upon entry of the foregoing amendments, Claims 1-13, 21-26, 46-53, and 66 will be pending. Currently, Claims 1-13 and 21-26 stand withdrawn and Claims 46-53 and 66 are presented for examination. Applicants added new Claim 66, which adds no new matter and support for which can be found, for example, in paragraphs [0056], [0110], and [0174].

The Examiner has rejected Claims 46-53. For the reasons set forth below, Applicants respectfully traverse and request withdrawal of the present rejections.

### Rejection Under 35 U.S.C. § 112, second paragraph - Definiteness

The Examiner has rejected Claims 52 and 53 as allegedly being indefinite under 35 U.S.C. § 112, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that “it is unclear from the claim and from applicant’s specification how the electrochemical signals are substantially free of guanine as guanine is a part of DNA.” *Office Action at 2.*

Applicants respectfully traverse. Claims 52 and 53 depend from Claim 51, which itself depends from Claim 46. Claim 51 specifies that the probe molecule is substantially free of polynucleotides having a length of at least 8 bases. Claim 52 further requires that the electrochemically active moiety of the probe is free of purines. Claim 53 adds the limitation that the electrochemical signals are substantially free from an oxidation or a reduction reaction of guanine.

As an initial matter, Applicants note that none of Claims 46, 51, or 52 requires that the probe be a polynucleotide, although that is an option supported by the specification. The probe could be, for example, an intercalating agent free of purines, such as is described in the specification in, e.g., paragraphs [0010] and [0116]. Such an intercalating agent would also be free of polynucleotides having a length of at least 8 bases, congruent with the limitation of Claim 51. Secondly, even if the probe is a polynucleotide, there is no requirement that the sequence include a purine base. For example, the sequence could be composed, for example, entirely of cytosine and/or thymine bases and further be free of polynucleotides having a length of at least 8 bases. Likewise, the probe could be entirely free of guanines, e.g., could be a nucleotide that

consists of adenine, thymine, and cytosine. This would allow for electrochemical signals that are “substantially free from an oxidation or a reduction reaction of guanine” as recited in Claim 53.

In view of the foregoing, Applicants respectfully submit that Claims 52 and 53 satisfy the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request reconsideration and withdrawal of the rejection accordingly.

Rejection Under 35 U.S.C. § 102(e) – Ito

The Examiner has rejected Claims 46 and 47 as allegedly being anticipated by U.S. Application Publication No. US 2002/0155477 to Ito. According to the Examiner, the Ito Application teaches an electrochemical method for detecting DNA hybridization comprising a first electrochemical signal from a first probe molecule in the presence of a first and a second polynucleotide, which are sufficiently complementary to form a duplex, and then subjecting the first and second polynucleotides to a heating step in the presence of the first amount of probe molecule and obtaining a second electrochemical signal from the probe molecule, thereby meeting each and every limitation of Claim 46. Regarding Claim 47, the Examiner states that Ito also teaches obtaining an electrochemical signal at a temperature below the melting point of the duplex and that double-stranded DNA can dissociate into single-stranded DNA at temperatures beyond a certain temperature, thereby meeting each and every limitation of Claim 47.

Applicants respectfully traverse. To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). “Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.” *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Applicants respectfully submit that Ito does not disclose each and every limitation of Claims 46 or 47, or, by extension, any claim that depends therefrom. Claim 46 recites “. . . a first amount of probe molecule in the presence of a first polynucleotide and a second polynucleotide, the first and second polynucleotides being sufficiently complimentary to form a duplex.” As such, there are three molecules present in the method of Claims 46 and 47: the first

polynucleotide, the second, complementary polynucleotide, and a probe. Ito fails to meet this limitation. Ito describes just two molecules – the probe and the target – involved in the detection process. (*See, e.g.*, Ito, paragraph [0041]). As such, Ito is not to be interpreted as reciting the three molecules (two complementary polynucleotides and a probe) claimed in Claim 46. In Ito, the probe is necessarily a single stranded polynucleotide complementary to the target. Ito describes the initial step in the gene detection process as “allowing a target gene to hybridize to the probe to form a double strand.” (Ito, paragraph [0041]). Elsewhere, Ito reiterates that “[t]he target gene is first hybridized to the probe . . . .” (Ito, paragraph [0085]). The target-probe hybridization is done prior to injecting the strands into the electrochemical detection container. (*See* Ito, paragraph [0085]). Thus, the method of Ito clearly does not include two complementary polynucleotides in the presence of an amount of probe molecule, as required by Claims 46 and 47. Accordingly, Ito cannot anticipate Claims 46 or 47 under 35 U.S.C. § 102.

Claim 47 further requires that “the first electrochemical signal is obtained at a temperature below the melting point of the duplex region and the second electrochemical signal is obtained at a temperature at least as great as the melting point of the duplex.” Ito fails to meet this limitation. In the Ito method, the “the target gene is first hybridized to the probe at a temperature lower than the target temperatures ( $T_i$ ) to form double strands.” (Ito, paragraph [0085]). Ito teaches raising the temperature of the “fully matched DNA . . . hybridized to the probe.” Thus, the Ito method involves obtaining the electrochemical signal of the probe hybridized to a single strand of DNA below the melting point and continuously raising the temperature until the  $T_m$  of the probe/target duplex is reached. The Ito method is in contrast to Claim 47, which claims that “the first electrochemical signal is obtained at a temperature below the melting point of the duplex.” In contrast to the Ito method, the “duplex” recited in Claim 47 is not the probe-target duplex, but a “duplex” of the first and second complementary polynucleotides of Claim 46. For this further reason, Ito fails to anticipate Claim 47.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) over Ito.

Rejection Under 35 U.S.C. § 103(a)

Claim 48 – Ito and Mathies

The Examiner has rejected Claim 48 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Ito in view of U.S. Patent No. 6,132,580 to Mathies et al. (“Mathies”). The Examiner states that Ito teaches an electrochemical detection means for genes, as discussed above but concedes that Ito does not specifically teach performing at least one amplification step between the first measurement of the duplex and the measurement of the duplex after a heating step. According to the Examiner, Mathies teaches PCR amplification and that PCR requires repeated cycling through a number of specific temperatures to carry out the melting, annealing, and ligation steps which are part of the process. The Examiner argues it would have been obvious to one skilled in the art to modify the method of detection in Ito to include an amplification step between the initial detection step and the heating step.

Applicants respectfully traverse. To establish a *prima facie* case of obviousness, the Examiner must establish that the prior art reference (or references when combined) must teach or suggest all of the claim limitations: “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Further, the Examiner must clearly articulate reasons why the claimed invention would have been obvious, with some rational underpinning to support the legal conclusion of obviousness, and taking into consideration how a person of ordinary skill would have understood the prior art teachings. (M.P.E.P. §2141). The art must be such that the skilled artisan would have a reasonable expectation of success at practicing the claimed invention. (M.P.E.P. §2143.02).

As set forth above with respect to Claim 46, Ito does not disclose an electrochemical detection method involving three molecules, *i.e.*, a first and a second polynucleotide and a probe, as required by Claim 46 and claims that depend therefrom. The Mathies reference does not cure the deficiencies of Ito. As with Ito, Mathies is completely silent regarding an electrochemical detection method that utilizes a first and second polynucleotide and a probe. In fact, Mathies is silent regarding the number of molecules involved in the detection process and whether the probe and target molecules start out in a hybridized state. Therefore, the references, either alone or in combination do not teach or fairly suggest each and every limitation of Claim 48. Further, the

references would not provide the skilled artisan with the requisite expectation of success. As such, Ito and Mathies cannot support a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 49 and 50 – Ito and Alvarez

The Examiner has rejected Claims 49 and 50 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Ito in view of Alvarez et al. (Electrochemistry Communications, 5, 2003, pages 267-271) (“Alvarez”). The Examiner’s assertions regarding the teachings of Ito are discussed above. The Examiner concedes that Ito does not specifically teach contacting the electrode with a liquid prior to obtaining a first electrochemical signal. The Examiner states that Alvarez teaches an electrochemical DNA biosensor in which the electrode is modified with probes, is dried, and then is contacted with water prior to obtaining a first signal. The Examiner argues it would have been obvious to one skilled in the art to modify the treatment of the electrode in Ito by contacting the dry electrode with a liquid prior to obtaining a first electrochemical signal as taught by Alvarez because providing a dry electrode will eliminate interference and will provide for enhanced hybridization detection.

Applicants respectfully traverse. As set forth above with respect to Claim 46, Ito does not disclose an electrochemical detection method involving three molecules, *i.e.*, a first and a second polynucleotide and a probe. The Alvarez reference does not cure the deficiencies of Ito. Specifically Alvarez is silent regarding the number of molecules involved in the detection process and whether the probe and target molecules start out in a hybridized state. Therefore, the references, either alone or in combination, do not teach or fairly suggest each and every limitation of Claims 49 and 50. Further, Ito and Alvarez do not provide the skilled artisan with the requisite expectation of success. As such, the references cannot support a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Claim 51 – Ito and Duong

The Examiner has rejected Claim 51 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Ito in view of U.S. Patent No. 6,740,518 to Duong et al. (“Duong”). The Examiner states that Ito teaches an electrochemical biosensor but does not specifically teach that the probe molecule is substantially free of polynucleotides having a length of at least 8 bases. The Examiner states that Duong teaches the point of attachment to the base will vary with the base and that attachment at any position is possible. The Examiner states that depending on the analyte of interest, the probe can be selected to comprise the desired number of bases. The Examiner argues it would have been obvious to one skilled in the art to modify the probe molecule in Ito to be any length except 8 bases, as taught by Duong, because the selection of the probe molecule with 5 or 6 bases will help to eliminate the effects of purines and guanine which preferably link via the 8 position.

Applicants respectfully traverse. As set forth above with respect to Claim 46, Ito does not disclose an electrochemical detection method involving three molecules, *i.e.*, a first and a second polynucleotides and a probe. The Duong reference does not cure the deficiencies of Ito. Specifically Duong is silent regarding the number of molecules involved in the detection process and whether the probe and target molecules start out in a hybridized state. Therefore, the references, either alone or in combination do not teach or fairly suggest each and every limitation of Claim 51, nor do they provide the skilled artisan with the requisite expectation of success. As such, Ito and Duong cannot support a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 52 and 53 – Ito, Duong, and Mascini

The Examiner has rejected Claims 52 and 53 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Ito and Duong in view of Mascini et al. (J. Anal. Chem., 2001, 369, pages 15-22) (“Mascini”). The Examiner states that Ito and Duong together teach an electrochemical biosensor in which the probe molecule is substantially free of polynucleotides having a length of at least 8 bases, but concedes that the references do not teach that the reaction is free from contribution of guanine. The Examiner states that Mascini teaches a biosensor that

utilizes a Ag/AgCl reference electrode as does Applicant's specification. The Examiner states that Mascini teaches that at a voltage of +1V guanine is oxidized and that the voltage can be varied so as to not provide for the guanine oxidation peak. The Examiner argues it would have been obvious to one skilled in the art to modify the voltage applied in Ito to fall within a range that is outside of the guanine oxidation peak which is around 1V as taught by Mascini because utilizing a voltage outside of the peak guanine range will help avoid interference by guanine in the electrochemical measurement.

Applicants respectfully traverse. As set forth above with respect to Claim 51, neither Ito nor Duong disclose an electrochemical detection method involving three molecules, *i.e.*, a first and a second polynucleotides and a probe. The Mascini reference does not cure the deficiencies of Ito or Duong. As with Ito and Duong, Mascini is silent regarding the number of molecules involved in the detection process and whether the probe and target molecules start out in a hybridized state. Therefore, the references, either alone or in combination do not teach or suggest each and every limitation of Claims 52 and 53, or provide the skilled artisan with the requisite expectation of success. As such, the combination of Ito, Duong and Mascini cannot support a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

*No Disclaimers or Disavowals*

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

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**CONCLUSION**

In view of the above remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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